F ENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 01 March 2001 (01.03.01)	
International application No. PCT/US00/15828	**Applicant's or agent's file reference** 03063-0590WP
International filing date (day/month/year) 08 June 2000 (08.06.00)	**Priority date** (day/month/year) 09 June 1999 (09.06.99)
Applicant POPE, Victoria et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

04 January 2001 (04.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

C. Cupello

Telephone No.: (41-22) 338.83.38

P. ENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

NOONAN, William, D.
Klarquist Sparkman Campbell Leigh & Whinston, LLP
One World Trade Center
Suite 1600
121 S.W. Salmon Street
Portland, OR 97204
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)
09 January 2001 (09.01.01)

Applicant's or agent's file reference
03063-0590WP

IMPORTANT NOTIFICATION

International application No.
PCT/US00/15828

International filing date (day/month/year)
08 June 2000 (08.06.00)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address

PRIOR, Kimberly, J.
Jones & Askew, LLP
2400 Monarch Tower
3424 Peachtree Road, N.E.
Atlanta, GA 30326
United States of America

State of Nationality

State of Residence

Telephone No.
(404) 949-2400

Facsimile No.
(404) 949-2499

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address

NOONAN, William, D.
Klarquist Sparkman Campbell Leigh & Whinston, LLP
One World Trade Center
Suite 1600
121 S.W. Salmon Street
Portland, OR 97204
United States of America

State of Nationality

State of Residence

Telephone No.
503 226-7391

Facsimile No.
503 228-9446

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

C. Cupello

Telephone No.: (41-22) 338.83.38

Jodie

PATENT COOPERATION TREATY

by fax and post

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

NOONAN, William D.
KLARQUIST, SPARKMAN, CAMPBELL,
LEIGH & WHINSTON, L.L.P.
One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
ETATS-UNIS D'AMERIQUE

001-503-228-9446

PREVIOUSLY DOCKETED
7/18/01

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	18.05.2001
Applicant's or agent's file reference: 6395-56706	**REPLY DUE** **within 2 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/15828	08/06/2000	09/06/1999

International Patent Classification (IPC) or both national classification and IPC

G01N33/571

Applicant

THE GOVERNMENT OF THE UNITED STATES OF AMERICA;

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☒	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 09/10/2001.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Bigot-Maucher, C

Formalities officer (incl. extension of time limits)
Neumann, M
Telephone No. +49 89 2399 7351

I. Basis of the opinion

1. With regard to the **elements** of the international application (Replacement *sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

   Description, pages:

   1-27 as originally filed

   Claims, No.:

   1-21 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-6, 9, 11-15, 20-21
Inventive step (IS)	Claims	7-8, 10, 16-19
Industrial applicability (IA)	Claims	

2. Citations and explanations
   see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Item V:

Reference is made to the following documents:

D1: US-A-4 307 074
D2: BRITISH JOURNAL OF CANCER,
vol. 74, no. 1, 1996, pages 43-48
D3: GB-A-1 053 504
D4: CHEMISTRY AND PHYSICS OF LIPIDS,IR,LIMERICK,
vol. 3, no. 1, 1969, pages 70-77
D5: TECHNICAL BULLETIN OF THE REGISTRY OF MEDICAL TECHNOLOGISTS,
vol. 3, October 1963, pages 171-176

The documents D6-D7 were not cited in the international search report. Copies of the abstracts are appended hereto.

D6: IMMUNOL SER,
vol 52, 1990, pp 101-124; abstract
D7: ANN PHARM FR,
col 57, no 1, 1999, pp 68-75; abstract

1. Articles 33(2) and (3) PCT

1.1. The subject-matter of claim 1 relates to an antigen composition comprising synthetic cardiolipin and synthetic lecithin. Since the claim does not provide a more specific determination of said synthetic substances, it includes any cardiolipin and lecithin which are produced artificially. Even natural cardiolipin and lecithin fall under the scope of the claim, since cardiolipin and lecithin can have been produced artificially with the same structure as the natural ones, i.e. no distinction of the products is possible. A compound is not rendered novel merely by the fact that it is produced by means of a new process.
Therefore, prior art documents relating to artificial and/or natural cardiolipin and lecithin as well as simply relating to any cardiolipin and lecithin without specifying

the source, are novelty destroying for claim 1:

D1 discloses an ethanolic solution of sodium D, L(2, 3-di-O-palmitoylglycerol) benzylphosphoric acid as synthetic cardiolipin, egg lecithin and cholesterol (col 4, example).

D2 describes a solution comprising tetramyristoyl cardiolipin, phosphatidylcholine and cholesterol dissolved in chloroform-methanol (p 44, I col, 3rd par).

D3 reveals an ethanolic solution comprising cardiolipin, cholesterol and lecithin (col 2, l 60-62).

D4 discloses an alcoholic solution containing cardiolipin, lecithin and cholesterol. In the case of synthetic cardiolipin tetrahydrofuran is used instead of alcohol (p 71, 4th par).

D5 describes the Kline cardiolipin-synthetic lecithin test (p 171, I col, 3rd par).

Thus, the subject-matter of **claim 1 is anticipated (Article 33(2) PCT)** by the disclosure of any one document D1-D5.

1.2. **The same applies to the following dependent claims**, as they only contain additional technical features which are also disclosed in any one document D1-D4:

- **claim 2**: D1, col 4, example; D2, abstr; D3, example 1; D4, p 71, 2nd par
- **claim 3**: D1, claim 7: 0.9 mg/ml; D3, example 1; D4, p 71, 4th par
- **claim 4**: D1, example, claim 5; D2, p 44, 3rd par, l 3; D3, example 1, l 39
- **claim 5**: D1, claim 6: 0.02mg/ml
- **claim 6**: D3, example 1; D4, p 71, 4th par
- **claim 9**: D2, abstr
- **claim 11**: D1, claim 5; D3, example 1, l 39

1.3. The subject-matter of **dependent claims 7-8 is novel**, since none of the prior art documents discloses the described concentrations.

However, the subject-matter of **claim 7 is not inventive (Article 33(3) PCT)**, since the skilled person is considered to be able to slightly modify this well known solution by use of conventional technology without an inventive concept: D1 discloses a value of 0.1mg/ml for lecithin (corresponding to 0.1% in the solution) which is considered to be very close at 1.1% lecithin disclosed in present claim 7. No particular technical effect is apparent from the minor concentration change of 0.01% of lecithin. Therefore, inventiveness cannot be acknowledged for claim 7.

The same applies to dependent claim 8 in view of D1. D1 discloses the use of 0.1-0.3 mg/ml of lecithin in the solution, which is considered to correspond to 0.1-0.3 %. Since no surprising technical effect seems to arise from the use of 0.14% of lecithin, said value is considered to be arbitrarily chosen from a known range and cannot confer to inventiveness.

1.4. The subject-matter of **dependent claim 10 appears to be novel** in the light of the prior art, since none of the documents discloses the claimed compound.

However, the subject-matter of **dependent claim 10 does not seem to be inventive**, since the additional feature of said dependent claim is considered purely conventional and does not lead to an unexpected effect (see also D1, col 4, l 25-26).

1.5. The subject-matter of independent claim 12 discloses a method for detecting the presence of Treponema pallidum, i.e. of syphilis, comprising combining a sample with the composition of present claim 1 and detecting an immunocomplex formed between an anti syphilis antibody present in the sample and the composition.

The method of **independent claim 12 is not considered novel** in the light of D1, D3, D4 or D5, since said documents already disclose the claimed method:

D1 discloses the determination of syphilis by detecting Wassermann antibodies (which are the classic cardiolipin antibodies in syphilis patients according to D6; see originally filed application, p 12, 1st par: also cardiolipin antibody detection) (claim 8) using a solution (col 4, example) as disclosed in claim 1 (see 1.1. herein

above) and determining the intensity of the immunological reaction (corresponds to immunocomplex formation between the antibody and the composition), i.e. the degree of flocculation occurring after the solution has been added (col 4, l 5-9).

D3 describes the determination of syphilis in a patient with an antigen agglutination test (p 1, l col, l 11-14) using a composition (cardiolipin and lecithin antigen) as claimed in claim 1 (see 1.1. herein above). The diagnostic test is based upon the known interaction of syphilis antigen with its corresponding antibody (p 1, l-r col, bridging sentence). The macroscopic agglutination of the particles indicates a positive reaction (p 2, l col, l 50-53), i.e. the anti-syphilis antibody is present in the sample.

D4 reveals a VDRL microflocculation test for testing the reactivity of sera against cardiolipin antigen (abstr). Cardiolipin antigen is the essential lipid in serodiagnosis of syphilis (p 70, l 1-2). A composition as claimed in present claim 1 (see 1.1.) is used for said test. Flocculation defines a positive result for syphilis (p 71, last lines).

D5 describes the classical cardiolipin-synthetic lecithin Kline test as well as other syphilis tests (p 175, summary) for the diagnosis of syphilis, i.e. a test using a composition as claimed in present claim 1. The Kline test is an agglutination test (see D7).

1.6. **The same applies to the following dependent claims**, as they only contain additional technical features which are also disclosed in any one document D1 and D3-D4:

- **claim 13**: D1, col 4, example; D3, example 1
- **claim 14**: D1, claim 7: 0.9 mg/ml; D3, example 1
- **claim 15**: D1, claim 5; D3, example 1, l 39
- **claim 20**: D1, D3-D5 (see summaries herein above)
- **claim 21**: D1, D4: flocculation; D3, D5: agglutination (see summaries herein above)

1.7. The subject-matter of dependent claims **16-17 and 19 appears to be novel, but not inventive** in analogy to dependent claims 7-8 and 10 (see 1.3.-1.4.).

1.8. The subject-matter of **dependent claim 18 appears to be novel**, since none of the prior art documents discloses a method for syphilis detection using said particular cardiolipin.

However, the subject-matter of **dependent claim 18 does not seem to be inventive** (Article 33(3) PCT), since the additional features of said dependent claim are purely conventional and do not seem to lead to an unexpected effect.

Item VII:

The vague and imprecise statement "spirit of the present invention" (p 18, l 5) implies that the subject-matter for which protection is sought may be different to that defined in the claims, thereby resulting in lack of clarity of the claims (Article 6 PCT) when used to interpret them (see the Guidelines, C-III, 4.3a). This statement should therefore be amended to remove inconsistency.

Concluding remarks:

Any new claims to be filed should take account of all of the above comments.

The applicant is requested to file amendments by way of replacement pages in the manner stipulated by Rule 66.8(a) PCT. In particular, fair copies of the amendments should be filed preferably in triplicate.

Moreover, the applicant's attention is drawn to the fact that, as a consequence of Rule 66.8(a) PCT the examiner is not permitted to carry out any amendments under the PCT procedure, however minor these may be.

In the reply, the parts of the application as originally filed which form a basis for the amendments (see Article 34(2)(b) PCT, last sentence) should be indicated.

PATENT COOPERATION TREATY

JL2 Klarquist

6395-56706

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

DOCKETED FOR 2.1701 1.1701

(PCT Rule 44.1)

COMPUTER ✓
CARD
BOOK ✓
DRAWER ✓
BKPR
ANN. SVE

To:
JONES & ASKEW, LLP
Attn. PRIOR, K.
2400 Monarch Tower
3424 Peachtree Road, N.E.
Atlanta, GA 30326
UNITED STATES OF AMERICA

RECEIVED
NOV 27 2000

Date of mailing *(day/month/year)*	17/11/2000
Applicant's or agent's file reference: 03063-0590WP	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No.: PCT/US 00/ 15828	International filing date *(day/month/year)*: 08/06/2000

Applicant

THE GOVERNMENT OF THE UNITED STATES OF AMERICA;

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Jaap Hurenkamp

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the International application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
03063-0590WP		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/ 15828	08/06/2000	09/06/1999
Applicant		
THE GOVERNMENT OF THE UNITED STATES OF AMERICA;		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   METHOD FOR DETECTING SYPHILIS USING SYNTHETIC ANTIGENS

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. --

   [ ] as suggested by the applicant.

   [ ] None of the figures.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/15828

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/571 G01N33/92

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

MEDLINE, CHEM ABS Data, EMBASE, SCISEARCH, EPO-Internal, WPI Data, PAJ, BIOSIS, COMPENDEX, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 307 074 A (BARNER RICHARD ET AL) 22 December 1981 (1981-12-22) example 1 claims ---	1-8, 10-17, 19-21
X	GOKHALE P C ET AL: "An improved method of encapsulation of doxorubicin in liposomes: Pharmacological, toxicological and therapeutic evaluation." BRITISH JOURNAL OF CANCER, vol. 74, no. 1, 1996, pages 43-48, XP000961424 ISSN: 0007-0920 abstract --- -/--	1-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 November 2000	17/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Muñoz, M

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 053 504 A (CHAS, PFIZER & CO.) 17 March 1964 (1964-03-17) example 1	1-8, 10-17, 19-21
X	INOUE K ET AL: "Immunochemical studies of phospholipids. IV. Reactivities of antiserum against natural cardiolipin and synthetic cardiolipin analogs-containing antigens" CHEMISTRY AND PHYSICS OF LIPIDS,IR,LIMERICK, vol. 3, no. 1, 1969, pages 70-77, XP000909168 ISSN: 0009-3084 the whole document	1-8, 10-17, 19-21
X	BROWNE A S ET AL: "AN EVALUATION OF THE CARDIOLIPIN - SYNTHETIC LECITHIN KLINE TEST." TECHNICAL BULLETIN OF THE REGISTRY OF MEDICAL TECHNOLOGISTS, vol. 3, October 1963 (1963-10), pages 171-176, XP000961563 the whole document	1,12
T	CASTRO ARNOLD R ET AL: "Use of synthetic cardiolipin and lecithin in the antigen used by the Venereal Disease Research Laboratory test for serodiagnosis of syphilis." CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, vol. 7, no. 4, July 2000 (2000-07), pages 658-661, XP000961557 ISSN: 1071-412X the whole document	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/15828

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4307074 A	22-12-1981	EP 0009088 A	02-04-1980
		JP 55042100 A	25-03-1980
GB 1053504 A		DE 1280585 B	
		FR 1455067 A	28-12-1966

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

NOONAN, William D.
KLARQUIST, SPARKMAN, CAMPBELL,
LEIGH & WHINSTON, L.L.P.
One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	08.08.2001
Applicant's or agent's file reference 6395-56706	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/15828	08/06/2000	09/06/1999

Applicant
THE GOVERNMENT OF THE UNITED STATES OF AMERICA;

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Danti, B Tel.+49 89 2399-8161

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
6395-56706		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/15828	08/06/2000	09/06/1999
International Patent Classification (IPC) or national classification and IPC G01N33/571		
Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA;		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04/01/2001	08.08.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Bigot-Maucher, C Telephone No. +49 89 2399 7415

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/15828

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-27 as originally filed

Claims, No.:

1-21 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7-8, 10, 16-19
	No:	Claims	1-6, 9, 11-15, 20-21
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-21
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Item V:

Reference is made to the following documents:

D1: US-A-4 307 074
D2: BRITISH JOURNAL OF CANCER,
vol. 74, no. 1, 1996, pages 43-48
D3: GB-A-1 053 504
D4: CHEMISTRY AND PHYSICS OF LIPIDS,IR,LIMERICK,
vol. 3, no. 1, 1969, pages 70-77
D5: TECHNICAL BULLETIN OF THE REGISTRY OF MEDICAL TECHNOLOGISTS,
vol. 3, October 1963, pages 171-176

The documents D6-D7 were not cited in the international search report:

D6: IMMUNOL SER,
vol 52, 1990, pp 101-124; abstract
D7: ANN PHARM FR,
col 57, no 1, 1999, pp 68-75; abstract

1. Articles 33(2) and (3) PCT

1.1. The subject-matter of claim 1 relates to an antigen composition comprising synthetic cardiolipin and synthetic lecithin. Since the claim does not provide a more specific determination of said synthetic substances, it includes any cardiolipin and lecithin having been produced artificially. Even natural cardiolipin and lecithin fall under the scope of the claim, since cardiolipin and lecithin can have been produced artificially with the same structure as the natural ones, i.e. no distinction of the products is possible. A compound is not rendered novel merely by the fact that it is produced by means of a new process.
Therefore, prior art documents relating to artificial and/or natural cardiolipin and lecithin as well as simply relating to any cardiolipin and lecithin without specifying the source, are novelty destroying for claim 1:

D1 discloses an ethanolic solution of sodium D, L(2, 3-di-O-palmitoylglycerol) benzylphosphoric acid as synthetic cardiolipin, egg lecithin and cholesterol (col 4, example).

D2 describes a solution comprising tetramyristoyl cardiolipin, phosphatidylcholine and cholesterol dissolved in chloroform-methanol (p 44, I col, 3rd par).

D3 reveals an ethanolic solution comprising cardiolipin, cholesterol and lecithin (col 2, l 60-62).

D4 discloses an alcoholic solution containing cardiolipin, lecithin and cholesterol. In the case of synthetic cardiolipin tetrahydrofuran is used instead of alcohol (p 71, 4th par).

D5 describes the Kline cardiolipin-synthetic lecithin test (p 171, I col, 3rd par).

Thus, the subject-matter of **claim 1 is anticipated (Article 33(2) PCT)** by the disclosure of any one of the documents D1-D5.

1.2. **The same applies to the following dependent claims**, as they only contain additional technical features which are also disclosed in any one document D1-D4:

- **claim 2**: D1, col 4, example; D2, abstr; D3, example 1; D4, p 71, 2nd par
- **claim 3**: D1, claim 7: 0.9 mg/ml; D3, example 1; D4, p 71, 4th par
- **claim 4**: D1, example, claim 5; D2, p 44, 3rd par, l 3; D3, example 1, l 39
- **claim 5**: D1, claim 6: 0.02mg/ml
- **claim 6**: D3, example 1; D4, p 71, 4th par
- **claim 9**: D2, abstr
- **claim 11**: D1, claim 5; D3, example 1, l 39

1.3. The subject-matter of **dependent claims 7-8 is novel**, since none of the prior art documents discloses the described concentrations.

However, the subject-matter of **claim 7 is not inventive (Article 33(3) PCT)**, since the skilled person is considered to be able to slightly modify this well known

solution by use of conventional technology without an inventive concept: D1 discloses a value of 0.1mg/ml for lecithin (corresponding to 0.1% in the solution) which is considered to be very close at 1.1% lecithin disclosed in present claim 7. No particular technical effect is apparent from the minor concentration change of 0.01% of lecithin. Therefore, inventiveness cannot be acknowledged for claim 7.

The same applies to dependent claim 8 in view of D1. D1 discloses the use of 0.1-0.3 mg/ml of lecithin in the solution, which is considered to correspond to 0.1-0.3 %. Since no surprising technical effect seems to arise from the use of 0.14% of lecithin, said value is considered to be arbitrarily chosen from a known range and cannot confer to inventiveness.

1.4. The subject-matter of **dependent claim 10 appears to be novel** in the light of the prior art, since none of the documents discloses the claimed compound.

However, the subject-matter of **dependent claim 10 does not seem to be inventive**, since the additional feature of said dependent claim is considered purely conventional and does not lead to an unexpected effect (see also D1, col 4, l 25-26).

1.5. The subject-matter of independent claim 12 discloses a method for detecting the presence of Treponema pallidum, i.e. of syphilis, comprising combining a sample with the composition of present claim 1 and detecting an immunocomplex formed between an anti syphilis antibody present in the sample and the composition.

The method of **independent claim 12 is not considered novel** in the light of D1, D3, D4 or D5, since said documents already disclose the claimed method:

D1 discloses the determination of syphilis by detecting Wassermann antibodies (which are the classic cardiolipin antibodies in syphilis patients according to D6; see originally filed application, p 12, 1st par: also cardiolipin antibody detection) (claim 8) using a solution (col 4, example) as disclosed in claim 1 (see 1.1. herein above) and determining the intensity of the immunological reaction (corresponds to immunocomplex formation between the antibody and the composition), i.e. the

degree of flocculation occurring after the solution has been added (col 4, l 5-9).

D3 describes the determination of syphilis in a patient with an antigen agglutination test (p 1, l col, l 11-14) using a composition (cardiolipin and lecithin antigen) as claimed in claim 1 (see 1.1. herein above). The diagnostic test is based upon the known interaction of syphilis antigen with its corresponding antibody (p 1, l-r col, bridging sentence). The macroscopic agglutination of the particles indicates a positive reaction (p 2, l col, l 50-53), i.e. the anti-syphilis antibody is present in the sample.

D4 reveals a VDRL microflocculation test for testing the reactivity of sera against cardiolipin antigen (abstr). Cardiolipin antigen is the essential lipid in serodiagnosis of syphilis (p 70, l 1-2). A composition as claimed in present claim 1 (see 1.1.) is used for said test. Flocculation defines a positive result for syphilis (p 71, last lines).

D5 describes the classical cardiolipin-synthetic lecithin Kline test as well as other syphilis tests (p 175, summary) for the diagnosis of syphilis, i.e. a test using a composition as claimed in present claim 1. The Kline test is an agglutination test (see D7).

1.6. **The same applies to the following dependent claims**, as they only contain additional technical features which are also disclosed in any one document D1 and D3-D4:

- **claim 13**: D1, col 4, example; D3, example 1
- **claim 14**: D1, claim 7: 0.9 mg/ml; D3, example 1
- **claim 15**: D1, claim 5; D3, example 1, l 39
- **claim 20**: D1, D3-D5 (see summaries herein above)
- **claim 21**: D1, D4: flocculation; D3, D5: agglutination (see summaries herein above)

1.7. The subject-matter of dependent claims **16-17 and 19 appears to be novel, but not inventive** in analogy to dependent claims 7-8 and 10 (see 1.3.-1.4.).

1.8. The subject-matter of **dependent claim 18 appears to be novel**, since none of

the prior art documents discloses a method for syphilis detection using said particular cardiolipin.

However, the subject-matter of **dependent claim 18 does not seem to be inventive** (Article 33(3) PCT), since the additional features of said dependent claim are purely conventional and do not seem to lead to an unexpected effect.

Item VII:

The vague and imprecise statement "spirit of the present invention" (p 18, l 5) implies that the subject-matter for which protection is sought may be different to that defined in the claims, thereby resulting in lack of clarity of the claims (Article 6 PCT) when used to interpret them (see the Guidelines, C-III, 4.3a). This statement has however not been amended to remove inconsistency.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
03063-0590WP		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/ 15828	08/06/2000	09/06/1999
Applicant		
THE GOVERNMENT OF THE UNITED STATES OF AMERICA;		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   METHOD FOR DETECTING SYPHILIS USING SYNTHETIC ANTIGENS

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. --

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/15828

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/571 G01N33/92

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

MEDLINE, CHEM ABS Data, EMBASE, SCISEARCH, EPO-Internal, WPI Data, PAJ, BIOSIS, COMPENDEX, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	GOKHALE P C ET AL: "An improved method of encapsulation of doxorubicin in liposomes: Pharmacological, toxicological and therapeutic evaluation." BRITISH JOURNAL OF CANCER, vol. 74, no. 1, 1996, pages 43-48, XP000961424 ISSN: 0007-0920 abstract --- -/--	1-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 November 2000	17/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Muñoz, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 053 504 A (CHAS, PFIZER & CO.) 17 March 1964 (1964-03-17) example 1	1-8, 10-17, 19-21
X	INOUE K ET AL: "Immunochemical studies of phospholipids. IV. Reactivities of antiserum against natural cardiolipin and synthetic cardiolipin analogs-containing antigens" CHEMISTRY AND PHYSICS OF LIPIDS,IR,LIMERICK, vol. 3, no. 1, 1969, pages 70-77, XP000909168 ISSN: 0009-3084 the whole document	1-8, 10-17, 19-21
X	BROWNE A S ET AL: "AN EVALUATION OF THE CARDIOLIPIN - SYNTHETIC LECITHIN KLINE TEST." TECHNICAL BULLETIN OF THE REGISTRY OF MEDICAL TECHNOLOGISTS, vol. 3, October 1963 (1963-10), pages 171-176, XP000961563 the whole document	1,12
T	CASTRO ARNOLD R ET AL: "Use of synthetic cardiolipin and lecithin in the antigen used by the Venereal Disease Research Laboratory test for serodiagnosis of syphilis." CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, vol. 7, no. 4, July 2000 (2000-07), pages 658-661, XP000961557 ISSN: 1071-412X the whole document	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/15828

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4307074 A	22-12-1981	EP 0009088 A	02-04-1980
		JP 55042100 A	25-03-1980
GB 1053504 A		DE 1280585 B	
		FR 1455067 A	28-12-1966

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
6395-56706		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/15828	08/06/2000	09/06/1999
International Patent Classification (IPC) or national classification and IPC G01N33/571		
Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA;		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04/01/2001	08.08.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Bigot-Maucher, C Telephone No. +49 89 2399 7415

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/15828

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-27 as originally filed

Claims, No.:

1-21 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7-8, 10, 16-19
	No:	Claims	1-6, 9, 11-15, 20-21
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-21
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Item V:

Reference is made to the following documents:

D1: US-A-4 307 074
D2: BRITISH JOURNAL OF CANCER,
vol. 74, no. 1, 1996, pages 43-48
D3: GB-A-1 053 504
D4: CHEMISTRY AND PHYSICS OF LIPIDS,IR,LIMERICK,
vol. 3, no. 1, 1969, pages 70-77
D5: TECHNICAL BULLETIN OF THE REGISTRY OF MEDICAL TECHNOLOGISTS,
vol. 3, October 1963, pages 171-176

The documents D6-D7 were not cited in the international search report:

D6: IMMUNOL SER,
vol 52, 1990, pp 101-124; abstract
D7: ANN PHARM FR,
col 57, no 1, 1999, pp 68-75; abstract

1. Articles 33(2) and (3) PCT

1.1. The subject-matter of claim 1 relates to an antigen composition comprising synthetic cardiolipin and synthetic lecithin. Since the claim does not provide a more specific determination of said synthetic substances, it includes any cardiolipin and lecithin having been produced artificially. Even natural cardiolipin and lecithin fall under the scope of the claim, since cardiolipin and lecithin can have been produced artificially with the same structure as the natural ones, i.e. no distinction of the products is possible. A compound is not rendered novel merely by the fact that it is produced by means of a new process.
Therefore, prior art documents relating to artificial and/or natural cardiolipin and lecithin as well as simply relating to any cardiolipin and lecithin without specifying the source, are novelty destroying for claim 1:

D1 discloses an ethanolic solution of sodium D, L(2, 3-di-O-palmitoylglycerol) benzylphosphoric acid as synthetic cardiolipin, egg lecithin and cholesterol (col 4, example).

D2 describes a solution comprising tetramyristoyl cardiolipin, phosphatidylcholine and cholesterol dissolved in chloroform-methanol (p 44, I col, 3rd par).

D3 reveals an ethanolic solution comprising cardiolipin, cholesterol and lecithin (col 2, l 60-62).

D4 discloses an alcoholic solution containing cardiolipin, lecithin and cholesterol. In the case of synthetic cardiolipin tetrahydrofuran is used instead of alcohol (p 71, 4th par).

D5 describes the Kline cardiolipin-synthetic lecithin test (p 171, I col, 3rd par).

Thus, the subject-matter of **claim 1 is anticipated (Article 33(2) PCT)** by the disclosure of any one of the documents D1-D5.

1.2. **The same applies to the following dependent claims**, as they only contain additional technical features which are also disclosed in any one document D1-D4:

- **claim 2**: D1, col 4, example; D2, abstr; D3, example 1; D4, p 71, 2nd par
- **claim 3**: D1, claim 7: 0.9 mg/ml; D3, example 1; D4, p 71, 4th par
- **claim 4**: D1, example, claim 5; D2, p 44, 3rd par, l 3; D3, example 1, l 39
- **claim 5**: D1, claim 6: 0.02mg/ml
- **claim 6**: D3, example 1; D4, p 71, 4th par
- **claim 9**: D2, abstr
- **claim 11**: D1, claim 5; D3, example 1, l 39

1.3. The subject-matter of **dependent claims 7-8 is novel**, since none of the prior art documents discloses the described concentrations.

However, the subject-matter of **claim 7 is not inventive (Article 33(3) PCT)**, since the skilled person is considered to be able to slightly modify this well known

solution by use of conventional technology without an inventive concept: D1 discloses a value of 0.1mg/ml for lecithin (corresponding to 0.1% in the solution) which is considered to be very close at 1.1% lecithin disclosed in present claim 7. No particular technical effect is apparent from the minor concentration change of 0.01% of lecithin. Therefore, inventiveness cannot be acknowledged for claim 7.

The same applies to dependent claim 8 in view of D1. D1 discloses the use of 0.1-0.3 mg/ml of lecithin in the solution, which is considered to correspond to 0.1-0.3 %. Since no surprising technical effect seems to arise from the use of 0.14% of lecithin, said value is considered to be arbitrarily chosen from a known range and cannot confer to inventiveness.

1.4. The subject-matter of **dependent claim 10 appears to be novel** in the light of the prior art, since none of the documents discloses the claimed compound.

However, the subject-matter of **dependent claim 10 does not seem to be inventive**, since the additional feature of said dependent claim is considered purely conventional and does not lead to an unexpected effect (see also D1, col 4, l 25-26).

1.5. The subject-matter of independent claim 12 discloses a method for detecting the presence of Treponema pallidum, i.e. of syphilis, comprising combining a sample with the composition of present claim 1 and detecting an immunocomplex formed between an anti syphilis antibody present in the sample and the composition.

The method of **independent claim 12 is not considered novel** in the light of D1, D3, D4 or D5, since said documents already disclose the claimed method:

D1 discloses the determination of syphilis by detecting Wassermann antibodies (which are the classic cardiolipin antibodies in syphilis patients according to D6; see originally filed application, p 12, 1st par: also cardiolipin antibody detection) (claim 8) using a solution (col 4, example) as disclosed in claim 1 (see 1.1. herein above) and determining the intensity of the immunological reaction (corresponds to immunocomplex formation between the antibody and the composition), i.e. the

degree of flocculation occurring after the solution has been added (col 4, l 5-9).

D3 describes the determination of syphilis in a patient with an antigen agglutination test (p 1, l col, l 11-14) using a composition (cardiolipin and lecithin antigen) as claimed in claim 1 (see 1.1. herein above). The diagnostic test is based upon the known interaction of syphilis antigen with its corresponding antibody (p 1, l-r col, bridging sentence). The macroscopic agglutination of the particles indicates a positive reaction (p 2, l col, l 50-53), i.e. the anti-syphilis antibody is present in the sample.

D4 reveals a VDRL microflocculation test for testing the reactivity of sera against cardiolipin antigen (abstr). Cardiolipin antigen is the essential lipid in serodiagnosis of syphilis (p 70, l 1-2). A composition as claimed in present claim 1 (see 1.1.) is used for said test. Flocculation defines a positive result for syphilis (p 71, last lines).

D5 describes the classical cardiolipin-synthetic lecithin Kline test as well as other syphilis tests (p 175, summary) for the diagnosis of syphilis, i.e. a test using a composition as claimed in present claim 1. The Kline test is an agglutination test (see D7).

1.6. **The same applies to the following dependent claims**, as they only contain additional technical features which are also disclosed in any one document D1 and D3-D4:

- **claim 13**: D1, col 4, example; D3, example 1
- **claim 14**: D1, claim 7: 0.9 mg/ml; D3, example 1
- **claim 15**: D1, claim 5; D3, example 1, l 39
- **claim 20**: D1, D3-D5 (see summaries herein above)
- **claim 21**: D1, D4: flocculation; D3, D5: agglutination (see summaries herein above)

1.7. The subject-matter of dependent claims **16-17 and 19 appears to be novel, but not inventive** in analogy to dependent claims 7-8 and 10 (see 1.3.-1.4.).

1.8. The subject-matter of **dependent claim 18 appears to be novel**, since none of

the prior art documents discloses a method for syphilis detection using said particular cardiolipin.

However, the subject-matter of **dependent claim 18 does not seem to be inventive** (Article 33(3) PCT), since the additional features of said dependent claim are purely conventional and do not seem to lead to an unexpected effect.

Item VII:

The vague and imprecise statement "spirit of the present invention" (p 18, l 5) implies that the subject-matter for which protection is sought may be different to that defined in the claims, thereby resulting in lack of clarity of the claims (Article 6 PCT) when used to interpret them (see the Guidelines, C-III, 4.3a). This statement has however not been amended to remove inconsistency.

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US 00/15828

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/571 G01N33/92

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
MEDLINE, CHEM ABS Data, EMBASE, SCISEARCH, EPO-Internal, WPI Data, PAJ, BIOSIS, COMPENDEX, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 307 074 A (BARNER RICHARD ET AL) 22 December 1981 (1981-12-22) example 1 claims ---	1-8, 10-17, 19-21
X	GOKHALE P C ET AL: "An improved method of encapsulation of doxorubicin in liposomes: Pharmacological, toxicological and therapeutic evaluation." BRITISH JOURNAL OF CANCER, vol. 74, no. 1, 1996, pages 43-48, XP000961424 ISSN: 0007-0920 abstract --- -/--	1-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 November 2000	17/11/2000

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/15828

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 053 504 A (CHAS, PFIZER & CO.) 17 March 1964 (1964-03-17) example 1	1-8, 10-17, 19-21
X	INOUE K ET AL: "Immunochemical studies of phospholipids. IV. Reactivities of antiserum against natural cardiolipin and synthetic cardiolipin analogs-containing antigens" CHEMISTRY AND PHYSICS OF LIPIDS,IR,LIMERICK, vol. 3, no. 1, 1969, pages 70-77, XP000909168 ISSN: 0009-3084 the whole document	1-8, 10-17, 19-21
X	BROWNE A S ET AL: "AN EVALUATION OF THE CARDIOLIPIN - SYNTHETIC LECITHIN KLINE TEST." TECHNICAL BULLETIN OF THE REGISTRY OF MEDICAL TECHNOLOGISTS, vol. 3, October 1963 (1963-10), pages 171-176, XP000961563 the whole document	1,12
T	CASTRO ARNOLD R ET AL: "Use of synthetic cardiolipin and lecithin in the antigen used by the Venereal Disease Research Laboratory test for serodiagnosis of syphilis." CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, vol. 7, no. 4, July 2000 (2000-07), pages 658-661, XP000961557 ISSN: 1071-412X the whole document	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern ial Application No
PCT/US 00/15828

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4307074 A	22-12-1981	EP 0009088 A	02-04-1980
		JP 55042100 A	25-03-1980
GB 1053504 A		DE 1280585 B	
		FR 1455067 A	28-12-1966